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**Opioids in dyspnoea: a prospective, multi-site, open label, dose increment, observational pharmacovigilance study.**

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## **Abstract**

### **Context**

Randomised controlled trials (RCTs) can answer questions of efficacy, but rarely generate a complete safety profile. Long term pharmacovigilance studies complement RCTs.

### **Objectives**

Level I evidence supports short term efficacy of opioids in reducing refractory dyspnoea. This study aims to determine: the minimum effective daily dose of sustained release morphine to reduce refractory breathlessness; and whether net clinical benefits are sustained safely.

### **Methods**

In a *phase II* dose increment study, 10mg sustained release morphine was administered daily, and increased by 10mg daily each week to a maximum of 30mg daily. The participant was withdrawn if there were unacceptable side-effects or no response to maximum dose. If participants had a 10% improvement in dyspnoea over their own baseline, they joined a long-term *phase IV* effectiveness/safety study at that dose. Complying with STROBE guidelines for reporting observational studies, response and side-effects are described, with demographic and clinical characteristics of responders.

### **Results**

Eighty five participants (65 males, mean age 74, 59% with chronic obstructive pulmonary disease (COPD) provided >30 patient-years of data. Fifty three participants derived  $\geq 10\%$  benefit (35.4% improvement over baseline) giving a response rate of 62% (number needed to treat of 1.6); for 70%, this dose was 10mg/24hours. Benefit was maintained at three months for 28 (33%) people. Breathlessness was reduced significantly ( $p < 0.001$ ) but constipation increased ( $p < 0.001$ ) despite aperients. There were no severe adverse events including no respiratory depression nor hospitalisations.

### **Conclusion**

Ten mg of sustained release oral morphine daily is safe in this population, and effective for most people.

**Key words:** Palliative care, Dyspnea, Opioids, Clinical effectiveness, Respiratory

**Running Title :** Opioid dose ranging and effectiveness

## Introduction

Randomised controlled trials can answer questions of efficacy, and although toxicities are reported, these studies are usually of the briefest duration in order to see a clinical benefit and rarely designed with power to detect significantly different levels of rare toxicities. The optimal way to answer questions of safety, sustained benefits and long term toxicities is through ongoing pharmacovigilance studies in order to understand the net clinical benefit in everyday practice. Pharmacovigilance studies are, by definition, uncontrolled studies.

Dyspnoea is more than a sentinel clinical sign; dyspnoea, experienced acutely or chronically, threatens a person's very existence, psychological well-being and social functioning. Once reversible causes of dyspnoea have been addressed, residual symptomatology is 'refractory dyspnoea'. [1]

At a population level, refractory dyspnoea is a significant chronic burden for a sizeable number of individuals. [2,3] Moreover, with many respiratory, cardiac, haematological, oncological and neuromuscular disorders, breathlessness is likely to worsen over time. [4] There are no symptom-specific medications to treat refractory dyspnoea registered with the major pharmaceutical regulatory bodies such as the Food and Drug Administration (FDA; USA), European Medicines Evaluation Agency (EMA; Europe) or Therapeutic Goods Administration (TGA; Australia).

Evidence, including an adequately powered randomised study and a meta-analysis, demonstrates that opioids reduce the intensity of refractory breathlessness. [1,5] The effect of opioids on the subjective sensation of breathlessness is further supported by recent evidence demonstrating that blockade of endogenous opioids during exercise worsens the perception of breathlessness without changing the ability to exercise in people with chronic obstructive pulmonary disease (COPD). [6]

While data supporting opioids for the treatment of refractory dyspnoea are clear, studies to date have not yet defined the minimum effective dose;[1,7,8] furthermore since the study by Abernethy et al which evaluated the efficacy of 20mg oral morphine daily, a 10mg per 24 hour preparation has become available.

Prospective data about long term safety is lacking. Many clinicians continue to extrapolate from the acute toxicity witnessed when frail or infirm opioid naïve patients were administered opioids in the emergency room or post-operatively, with severe side effects including confusion, drowsiness and respiratory depression.[9,10] These observations, first made more than six decades ago, still largely underpin the poor uptake of an entirely different way of prescribing opioids for refractory breathlessness - regular low doses. International guidelines for opioids in refractory breathlessness continue to reflect concerns generated by the way opioids are used for acute pain.[11,12] Lack of dosing and safety data continue to be a major barrier in the registration of a dyspnoea-related indication for morphine.

Given the chronic nature of breathlessness for many people, there are justifiable concerns that benefits of opioids may diminish over time. There have been no longitudinal, prospective data describing the net clinical benefits of low-dose opioids in people with chronic refractory dyspnoea.

The aims of the *phase II* exploratory open-label, dose-ranging study were to define the minimum dose of morphine for reducing chronic refractory dyspnoea by  $\geq 10\%$ ; a *phase IV* follow-on study sought to define the safety of daily sustained release morphine and longer-term clinical effectiveness. The best level of evidence for *phase IV* outcomes is generated by prospective cohort

data collection. Results complement current *phase III* evidence about the short-term efficacy of opioids in relieving breathlessness.

## **Methods**

### *Study Design*

This study comprised *phase II* and *IV* components (Figure 1). *Phase II* was an open label, prospective study of once-daily sustained-release opioid (morphine sulphate 10mg / 24 hours titrated weekly by 10mg / 24 hours in non-responders up to a maximum of 30mg / 24 hours) administered with aperients (sodium docusate with sennosides). If at any weekly review the participant had a reduction of  $\geq 10\%$  over baseline in dyspnoea intensity without side-effects, they entered the long-term safety and effectiveness *phase IV* study. Any unresolved significant side-effects at any time or a lack of response by the end of the three week titration during the *phase II* component of the study resulted in participant withdrawal from the study.

### *Study Participants*

Participants were opioid-naïve outpatients aged  $\geq 18$  years with breathlessness scored at  $\geq 2$  on the modified Medical Research Council (MRC) scale [13] (Table 1). Any underlying reversible causes of the dyspnoea must have been maximally treated, as assessed by a consultant physician whose area of practice was most relevant to the cause of this person's dyspnoea (e.g. a cardiologist for someone with cardiomyopathy). Participants must also have been on stable medications and oxygen (if required) for the seven days before commencing the study and an estimated prognosis of  $>1$  month.

Exclusion criteria included: regular use of any opioid medication in the two weeks before screening; a true hypersensitivity reaction to opioids; a history of substance misuse; use of

monoamine oxidase inhibitors in the last two weeks; functional status <50 on the Australian-modified Karnofsky Performance scale (AKPS) [14] (Table 2); a calculated creatinine clearance of less than 15ml/min (as calculated using the MDRD formula [15]); pregnancy; confusion (less than 24/30 on a Mini-Mental State Examination(MMSE) [16]); or unwilling or unable to complete the study measures.

### *Settings*

Participants were recruited from four tertiary university teaching hospitals in two states of Australia between July 2007 and October 2009. Data collection was completed in January 2010. Lead study investigators were respiratory and palliative medicine physicians although referrals were encouraged from all disciplines including cardiology and oncology.

### *Study Withdrawal*

Withdrawal from the study could be initiated at any time by the participant. Other reasons for withdrawal included AKPS [14] falling below 30, a sudden increase in dyspnoea, or participant death.

### *Measurements*

Intensity of dyspnoea was the primary outcome, measured as subjective breathlessness on a 100mm visual analogue scale (VAS) 'right now' anchored at 0mm as "no breathlessness" and at 100mm as "worst imaginable breathlessness". Participants recorded dyspnoea twice daily in a purpose-printed diary.

During the *phase II* dose-ranging sub-study, morning and evening dyspnoea VAS scores recorded on days 5-7 of each 7 day week (i.e., during steady state) were averaged and contributed to



assessments of the number of people who responded to morphine and the dose at which they responded; an individual improvement of 10% over baseline was considered, *a priori*, as a clinically significant improvement, consistent with previous studies of similar interventions.[1,5]

During the *phase IV* long-term effectiveness component of the study, the number of people still on opioids at three months, the dose of opioid at three months, and the number of dose changes since entry to this sub-study were recorded. Side-effects at any time causing cessation of the medication were a key secondary outcome.

#### *Data collection and data quality*

Data were collected, coordinated centrally by the lead site and entered contemporaneously on a customised 128-bit secure web-based research data management system ([www.caresearch.com.au](http://www.caresearch.com.au)) so any discrepancies could be addressed immediately.

#### *Sample size*

Given the overall health of the target population, it was expected that, on average, individuals would participate for 3 months. This study was pragmatically built around a goal of collecting 25 patient-years of data in the *phase IV* arm. During study planning, it was anticipated that this would require 100 participants to achieve this.

#### *Analysis*

Basic descriptive statistics were used to define the population and their response to opioids. Intensity of breathlessness was described at baseline, at completion or withdrawal from the *phase II* dose ranging period, and at three months or the last recorded level in the long-term *phase IV* effectiveness period. Comparisons were made of key demographic and clinical factors for people

who did and did not progress to the *phase IV* study using Chi-square tests. Significance was assumed at  $p < 0.05$ . A comparison of the number of people who rated breathlessness or constipation as one of their problems at the beginning and end of the study were compared using McNemar's test with continuity correction. To confirm the direction and magnitude of primary outcome, data were re-analysed using 15% and 20% improvements in dyspnoea at the end of *phase II*.

### *Ethics, consent and trial registration*

The research was approved by all participating institutions' Research and Ethics Committees. All participants provided written informed consent before participating in the study. The study received Clinical Trials Notification approval to use Kapanol<sup>TM</sup> for an unregistered indication. The trial was registered with the Australian and New Zealand Clinical Trials Registry (ACTRNO12606000269538).

### *Reporting*

This paper complies with the STROBE reporting requirements for observational studies.[17]

## **Results**

### *Participant Flow and Study Population*

A total of 202 people with dyspnoea were screened and 85 participated in the study (Figure 2). Participant characteristics are summarised in Table 2.

### *Phase II Dose Ranging*

At the end of the *phase II* period, the average VAS score for intensity of dyspnoea had fallen from a baseline of 51.9mm (Standard deviation (SD) 19.2; median 56.8; range 11.0-81.3) to 40.2 (SD

20.1; median 39.8; range 1.8 – 86.5) for all 85 participants the mean sustained release morphine dose was 16.6mg (SD 8.1; median 10.0). Thirty two participants either derived no benefit at the maximum dose of 30mg of sustained release morphine (n=9), lacked benefit at other doses (n=3), had unacceptable side-effects (n=15), or withdrew for reasons other than the therapy (death n=4, clinical request n=1). (Figure 2) For the 15 with side-effects, these included; drowsiness (n=4); confusion (n=3); and constipation (n=2; Figure 2) all of which reversed rapidly with cessation of medication. No one required hospitalisation for any toxicity.

On an intention-to-treat basis, the response rate at the end of the *phase II* period was 53/85 (62%), giving a number needed to treat of 1.6, and a number needed to harm of 4.5. If, in the *phase II* period of the study, the clinical response threshold indicating successful therapeutic response was increased to 15% or 20% improvement over baseline dyspnoea scores, then 43 individuals (54%) and 35 individuals (44%) respectively, would have met these revised response criteria.

#### *Phase IV Long-term Effectiveness*

A total of 53 participants derived at least a 10% improvement over their own baseline breathlessness without unacceptable side-effects and proceeded to the long-term *phase IV* effectiveness period, on an average dose of 14.0mg (SD 6.3) of sustained release morphine sulphate per 24 hours. (Table 3)

Of the responders, 70% had benefit at 10mg of sustained release morphine in 24 hours, 23% at 20mg, and 8% at 30mg. For people entering the *phase IV* period, the average improvement in scores from their own baselines as they entered *phase IV* was 17.5mm (SD 11.7). (Table 3) A total of 29.5 years of data were collected in the *phase IV* period (mean 205.6 patient days per participant entering the *phase IV* period) within a total of 32.5 patient years of data overall.

Withdrawal from the *phase IV* study included 15 people who withdrew because of side effects (constipation (n=6); drowsiness (n=4); nausea (n=3); and vomiting (n=2) (Figure 2)) within the first three months. All side-effects settled rapidly with cessation of opioids, and no hospitalisations were required. Additionally, three participants required increased opioid doses for pain, two participants died as a result of disease progression during follow-up, and three identified that clinical benefit had waned. One participant had a single episode of urinary retention that did not necessitate study withdrawal but may have been caused or exacerbated by the anti-cholinergic effects of morphine.

At three months after commencing *phase IV*, of the 24 people still taking opioids for breathlessness and keeping a diary, 12 were taking 10mg of sustained release morphine per 24 hours and 12 were taking 20mg. Nineteen were on the same dose from which they left the *phase II* dose-ranging study period, 4 had increased their dose by 10mg/24hours, and one had decreased their dose by 10mg/24hours. Another 4 participants continued on their sustained release opioid but did not continue their diary.

#### *Patient-identified problems - breathlessness*

Using any of the first three ranked problems identified by participants on the Magill Quality of Life scale at baseline and on completion of the study or withdrawal, there was a significant decline in reports of breathlessness and significant increase in the number of people who were constipated. (Table 4)

None of the following factors identified individuals more likely to benefit from opioids and to progress to the *phase IV* period of the study: gender, age ( $\leq 75$  or greater), baseline MRC scores (4 versus 2,3), baseline VAS severity ( $\leq 60$  or greater), AKPS (40,50 versus  $\geq 60$ ), Magill Quality of Life at baseline ( $\leq 5$  versus  $> 5$ ), BMI ( $\leq 25$  versus  $> 25$ ), nor primary diagnosis (cancer / non-

cancer). Since potential univariate predictors were not significant, a multivariable model was not created.

### *Toxicity*

No study participants presented to healthcare providers: none were hospitalised for respiratory depression, decreased level of consciousness or delirium. People who chose to cease their sustained release morphine because of lack of effect or side-effects did so without a withdrawal syndrome.

## ***Discussion***

### *Principal findings*

This study confirms that some people respond to opioid therapy when administered for refractory breathlessness, and that the benefit can be maintained over time. Despite concerns about treating infirm, elderly individuals with opioids, study participants did not encounter severe toxicity; while some side-effects did occur, these were a rare occurrence and resolvable. Because morphine is excreted by the kidneys changes in renal function should prompt re-evaluation of dosing in the chronic setting. Opioids provide net clinical benefits in this setting having accounted for unwanted side-effects, especially since all side-effects were quickly reversed with dose reduction or medication cessation. Given knowledge of the metabolism of opioids, changes in renal function on a stable dose of opioids would be one such concerning scenario. The net clinical benefit is in favour of the use of opioids in this setting especially considering that any side-effects were rapidly reversed with dose reduction or cessation.

It needs to be emphasised that the way opioids have been used in this study is distinctly different to the way that they are used for acute pain in opioid naïve patients. Opioids were administered as

around-the-clock steady state dosing, more consistent with the management of chronic pain in opioid-tolerant patients.

Is the reduction in breathlessness clinically significant? Beyond evaluating whether patients consider the net clinical benefit sufficient to continue a therapy, there are several ways that minimal clinically important differences have been approached in the literature: statistically using distribution estimates; expert consensus opinion, patient preference; and anchor approaches.[18] A reduction in an observation by a level of greater than 50% of the standard deviation of the original observation is likely to be meaningful in measures such as quality of life.[19] In this study, the initial standard deviation of the observation was 19.2mm, so any reduction of greater than 9.6mm would exceed a 50% reduction in the standard deviation of the initial observation. The overall reduction in breathlessness for all 85 participants (responders and non-responders) at the end of the titration period was 11.7mm on the VAS, or a 61% reduction, suggesting that this is likely to be clinically significant.

*What other conclusions do these data support?*

These data are consistent with a mediating role of opioids in people with refractory dyspnoea without compromising respiratory function,[6,20] and are consistent with *phase III* studies that have been reported to date.[1,5] This current study supports the use of opioids for longer periods of time with no clinically significant respiratory compromise, and no evidence of tachyphylaxis.

*Do these findings differ from any other reported data?*

These data challenge widely held beliefs that opioids should not be used in people with respiratory compromise. Such beliefs are *not* based on data from people on regular low dose opioids, and, in fact, none of the study participants had an episode of respiratory compromise. The data also

challenges concerns about the withdrawal of opioids when they are no longer effective or not wanted.

#### *Strengths of the study*

The study, spread across four sites with differing referral patterns, can be extrapolated to other clinical settings. The study followed people closely throughout the time that they were on opioids, without loss to follow-up. The primary outcome measure of intensity of breathlessness is the primary concern of people with ongoing refractory breathlessness.

#### *Limitations of the study – design*

The threshold of 10% for response was arbitrary. When other thresholds were considered in a sensitivity analysis, at 15% and 20% there are still a substantial number of people who derive benefit from opioids. The absence of end-tidal carbon dioxide measurement or oxygenation is unfortunate, but the absence of significant respiratory compromise is reassuring. However the study was designed during a time when easily portable, affordable, community-based assessment of end-tidal carbon dioxide was not available and it was felt that the burden of arterial blood gas measurements in this patient group was not supportable. Dose titration stopped at 30mg per 24 hours given the levels of toxicity reported in a earlier study that used higher doses of opioids in the chronic setting.[21]

These results may under-represent the net clinical benefit. As with pain, people may increase activity as the symptom is better controlled but report only marginal improvement in the symptom itself. As such, future work in this area needs to have a meticulous understanding of differential changes in functional status over each person's own baseline.

### *Limitations of the study - sample*

People with heart failure are under-represented in the sample, and given encouraging evidence that they may be a diagnostic group who may respond well to opioids for their refractory dyspnoea, this is not ideal.[22,23] The sample deliberately did not engage people with acute exacerbations of breathlessness, although this would be an area for future research.

### *Generalizability*

This study represents findings from several sites with people whose unifying feature is the severity of their breathlessness. Fundamentally, there is a question of whether underlying pathologies generate distinct types of breathlessness that are equally responsive to opioids. Whether the underlying aetiology of breathlessness is sufficiently uniform to allow interchangeability of symptomatic therapies between differing pathologies is not finally determined. The predominant diagnosis was people with COPD, the area in which most work has been done in breathlessness to date.[6,24]

### *Implications for clinicians and policymakers*

This study adds to the weight of evidence that opioids can be used judiciously in people with refractory breathlessness without compromising their health. Benefit was sustained in more than half of the people who gained an initial response without undue side-effects. The majority of the follow-up was done by general practitioners in the community and these should be the practitioners who manage dyspnoea using opioids in the future.

### *Unanswered questions and future research*

These data support the need for a subsequent study exploring whether incremental dose increases in opioid responders would provide further symptom relief and hence a dose-response relationship.



Future work with opioids also needs to distinguish between changes in the intensity of breathlessness and the affect of unpleasantness that it engenders, and seek to compare the net clinical benefit of different opioids. Non-invasive measures of changes in the partial pressure of carbon dioxide and oxyhaemoglobin saturation in the first days of dose initiation or dose increment should be monitored.

The study highlights a key challenge for many new therapies – it is not practicable to power adequately rigorous studies for an expected but extremely rare toxicity. Although respiratory depression is the key concern in prescribing opioids for breathlessness, powering a study for safety with a very rare event as the basis for the sample size calculation is very difficult. This study underscores the need for good, publically available, and routinely collected pharmacovigilance studies for all therapies, including opioids in breathlessness.[25]

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**Table 1 – Modified Medical Research Council (MRC) Dyspnea Scale<sup>13</sup>**

<b>Grade</b>	<b>Description of symptom</b>
0	“I only get breathless with strenuous exercise”
1	“I get short of breath when hurrying on the level or walking up a slight hill”
2	“I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level”
3	“I stop for breath after walking about 100 yards or after a few minutes on the level”
4	“I am too breathless to leave the house” or “I am breathless when dressing”

Note: This modified MRC scale uses the same descriptors as the original MRC scale in which the descriptors are numbered 1-5.

**Table 2 – Characteristics of participants**

		<b>n</b>	<b>%</b>		
Gender	Male	55	65		
Diagnosis	Chronic obstructive pulmonary disease	50	59		
	Lung cancer	19	22		
	Interstitial lung disease	10	12		
	Other causes	6	7		
		<b>Mean</b>	<b>Standard deviation</b>	<b>Median</b>	<b>Range</b>
Age		74	8.8		51-88
Dyspnoea score (100mm visual analogue scale (VAS))		51.9	19.2	56.8	11.0-81.3
Modified Medical Research Council Scale (mMRC)		3.7	0.4	4.0	2-4
Australian-modified Karnofsky Performance Status (0-100)		63.1	60.0	9.49	40-80
Body Mass Index (BMI)		24.9	24.9	9.1	14.2-38.4
Magill Quality of life global rating (0-10)		5.9	6.0	2.1	0-10
Participation in study (days)		139	189	25	2-665



**Table 3 - *Phase IV* long term effectiveness study of people who have responded to once daily sustained release morphine for refractory dyspnoea (n=53).**

	Mean	Standard deviation	Median	Range
VAS as participants enter <i>phase IV</i> study	34.5	17.1	38.0	1.8-70.5
Improvement (mm on VAS entering <i>phase IV</i> study) from baseline	17.5	11.7	13.5	2.2-61.6
Individual percentage improvement over baseline entering <i>phase IV</i> study*	35.4	21.1	30.3	10.1-85.74
Dose of sustained release morphine (mg/24 hours) entering <i>phase IV</i> (n=53)	14.0	6.3	10.0	10 – 30
Magill Quality of life global rating (0-10)	6.1	6.0	2.0	0-10

\*Equals baseline dyspnoea minus final dyspnoea divided by baseline dyspnoea

**Table 4 – Participant ranked ‘physical symptoms or problems which have been the biggest problem for you over the past two (2) days’ at baseline and when last recorded from the Magill Quality of Life Questionnaire.**

		First ranked symptom concern	p value**	Symptom of concern ranked in the top three	p value
Breathlessness	Baseline n = 85	75	<0.001	80	<0.001
	Last recorded n = 81*	40		56	
Constipation	Baseline n = 85	0	<0.001	8	<0.001
	Last recorded n = 81*	14		27	

\*Four participants died during the initial titration disease for reasons unrelated to the study medication, and one person withdrew before taking any medication.

\*\* McNemar’s Chi Squared test with continuity correction